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Comparison of Outcome After Percutaneous Mitral Valve Repair With the MitraClip in Patients With Versus Without Atrial Fibrillation

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Percutaneous mitral valve repair with the MitraClip is an established treatment for patients with mitral regurgitation (MR) who are inoperable or at high risk for surgery. Atrial Fibrillation (AF) frequently coincides with MR, but only scarce data of the influence of AF on outcome after MitraClip is available. The aim of the current study was to compare the clinical outcome after MitraClip treatment in patients with versus without atrial fibrillation. Between January 2009 and January 2016, all consecutive patients treated with a MitraClip in 5 Dutch centers were included. Outcome measures were survival, symptoms, MR grade, and stroke incidence. In total, 618 patients were treated with a MitraClip. Patients with AF were older, had higher N-terminal B-type natriuretic peptide levels, more tricuspid regurgitation, less often coronary artery disease and a better left ventricular function. Survival of patients treated with the MitraClip was similar for patients with AF (82%) and without AF (non-AF; 85%) after 1 year (p = 0.30), but significantly different after 5-year follow-up (AF 34%; non-AF 47%; p = 0.006). After 1 month, 64% of the patients with AF were in New York Heart Association class I or II, in contrast to 77% of the patients without AF (p = 0.001). The stroke incidence appeared not to be significantly different (AF 1.8%; non-AF 1.0%; p = 0.40). In conclusion, patients with AF had similar 1-year survival, MR reduction, and stroke incidence compared with non-AF patients. However, MitraClip patients with AF had reduced long-term survival and remained more symptomatic compared with those without AF. **(Am J Cardiol 2017;120:2035–2040)**

Percutaneous mitral valve repair with the MitraClip is an established treatment for patients with mitral regurgitation (MR) who are inoperable or at high risk for surgery.[1–3] Atrial fibrillation (AF) frequently coincides with MR.[4] AF is common in the general population, with a prevalence increasing with age.[5–7] Population-based studies indicate an impaired long-term survival and an increased risk of stroke in patients with AF compared with patients without AF (or non-AF).[8–11] In some studies, the outcome of surgical mitral valve repair in patients with AF was similar compared with patients without AF,[12,13] in contrast to some surgical studies that reported worse outcomes for patients with AF.[14–16] Conflicting results have also been reported about the impact of AF on the outcome of MitraClip implantation.[17–20] The aim of the current study was to compare in a large-scale study the clinical outcome after percutaneous mitral valve repair with the MitraClip in patients with versus without atrial fibrillation.

Methods

Between January 2009 and January 2016, all 618 consecutive patients treated with a MitraClip in 5 Dutch centers were included. Preprocedural evaluation included physical examination, electrocardiography, transthoracic echocardiography (TTE), transesophageal echocardiography, and laboratory measurements. Patients were judged in a heart team consisting of an interventional cardiologist, an imaging cardiologist, and a cardiac surgeon. All patients had symptomatic MR and were rejected for surgery. Main exclusion criteria for MitraClip treatment were an unsuitable mitral valve anatomy or a life expectancy assessed as below 12 months due to severe comorbidities. Thirty-nine patients who did not receive a MitraClip during the implantation procedure were excluded from the analyses.

The MitraClip procedure has previously been described.[1,21] The procedure was performed under general anesthesia, using

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See page 2039 for disclosure information.

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fluoroscopic and transesophageal echocardiographic guidance. The results of MitraClip implantation were evaluated by TTE at discharge and during follow-up. All patients gave their written informed consent. The study complied with the ethical guidelines of the 1975 Declaration of Helsinki regarding investigation in humans.

The baseline characteristics of 618 patients were entered into the dedicated, prospective web-based database. All patients were invited for clinical evaluation and TTE at 1 month, 6 months, and 12 months after MitraClip implantation. The stroke incidence was documented over the full follow-up period. Symptoms of dyspnea were quantified using the New York Heart Association (NYHA) classification. MR severity was graded as none, mild (1), moderate (2), moderate to severe (3), or severe (4) by experienced echocardiographers. Patients were followed-up until either their death, or until March 1, 2016.

Continuous variables were expressed as mean ± standard deviation or as median and interquartile range. Categorical variables were presented as absolute numbers and percentages. Survival was described using the Kaplan-Meier method. Multivariable Cox regression, using stepwise forward selection, was performed to analyze the association of clinical characteristics with survival, expressed as hazard ratio (HR) with 95% confidence interval (CI) and p values. Confounders-adjusted logistic regression analysis was used for binary data and expressed as odds ratios with 95% CI and p values. McNemar's test was used to compare paired categorical data. Chi-square testing was used to compare unpaired categorical data. An unpaired *t* test was used to compare continuous variables when normally distributed and a Mann-Whitney *U* test when not normally distributed. Differences were considered statistically significant at p values <0.05. All statistical analyses were performed using SPSS software (IBM SPSS Statistics version 23, IBM Corp, Armonk, New York).

Results

In total, 618 patients were treated with the MitraClip. Baseline characteristics were generally comparable between patients with and without AF (Table 1), except that patients with AF were older (p <0.001), had higher levels of N-terminal pro-B-type natriuretic peptide (NT-proBNP) (p <0.001), and had more often a tricuspid regurgitation grade 4 (p = 0.045). Furthermore, patients without AF had more often coronary artery disease (p = 0.02) and an impaired left ventricular function (p <0.001).

The number of implanted MitraClips was similar for patients with and without AF (p = 0.19). Summarizing, 351 (57%) patients were treated with 1 MitraClip and 267 (43%) with ≥2 MitraClips. The use of ≥2 MitraClips changed over time, with 29% in the first one-third and 54% in the last one-third of the patients. MR grade 1 or 2 after MitraClip procedure was 79% for patients with AF and 82% for patients without AF (p = 0.36). The recurrent MR rate, defined as recurring to MR grade 3 or 4 during the first 12 months, was also similar for patients with (32%) and without AF (30%) (p = 0.74).

The median follow-up duration was 1.8 years. The survival estimate after 1 year was similar for patients treated with the MitraClip with AF (82%) and without AF (85%) (p = 0.30). However, the survival estimate after 5 years was significantly different (AF 34%, non-AF 47%, p = 0.006) (Figure 1).

Table 1
Baseline characteristics

Variable	All patients (n = 618)	Atrial fibrillation		p value
		No (n = 292)	Yes (n = 326)	
Age at procedure (years)	74 ± 11	71 ± 11	76 ± 9	<0.001
Men	353 (57%)	168 (58%)	185 (57%)	ns
Logistic European System for Cardiac Operative Risk Evaluation (%)	19.6 ± 14.2	19.3 ± 14.1	19.8 ± 14.3	ns
Chronic obstructive pulmonary disease	128 (21%)	64 (22%)	64 (20%)	ns
Coronary artery disease	357 (58%)	183 (63%)	174 (53%)	0.02
Cardiac implantable electronic devices	192 (31%)	94 (32%)	98 (30%)	ns
Diabetes Mellitus	142 (23%)	73 (25%)	69 (21%)	ns
Hypertension	322 (52%)	146 (50%)	176 (54%)	ns
Previous coronary artery bypass graft	185 (30%)	91 (31%)	94 (29%)	ns
Previous percutaneous coronary intervention	178 (29%)	90 (31%)	88 (27%)	ns
Previous stroke	71 (12%)	38 (13%)	33 (10%)	ns
Previous valve surgery	43 (7%)	15 (5%)	28 (9%)	ns
New York Heart Association class ≥III/IV	538 (87%)	250 (86%)	288 (88%)	ns
N-terminal pro-B-type natriuretic peptide (ng/L)	1642 (600–3669)	1135 (417–3253)	1905 (864–4072)	<0.001
Estimated glomerular filtration rate (ml/min/1.73 m^2)	56 ± 23	58 ± 24	54 ± 22	ns
Echocardiographic variables				
Mitral regurgitation grade 4	406 (66%)	203 (70%)	203 (62%)	ns
Tricuspid regurgitation grade 4	62 (10%)	22 (8%)	40 (12%)	0.045
Mitral regurgitation etiology				ns
Degenerative	126 (20%)	55 (19%)	71 (22%)	
Functional	456 (74%)	225 (77%)	231 (71%)	
Mixed	36 (6%)	12 (4%)	24 (7%)	
Impaired left ventricular function (<30%)	227 (37%)	130 (45%)	97 (30%)	<0.001

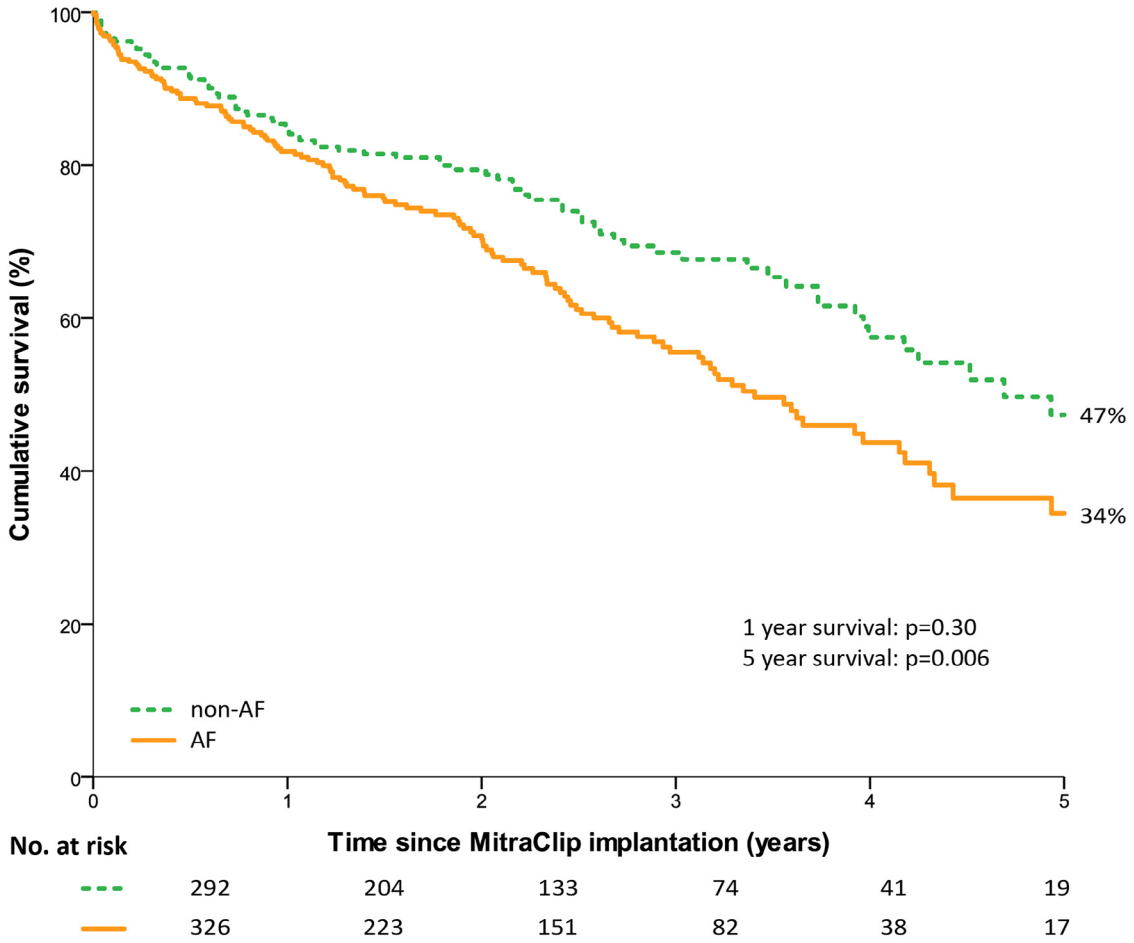

Figure 1. Survival after MitraClip implantation. The survival of patients with (n = 326) and without (n = 292) AF treated with MitraClip. AF = atrial fibrillation.

Multivariable Cox regression showed that age ≥80 years (HR 2.8, 95% CI 1.4 to 5.7), male gender (HR 1.4, 95% CI 1.0 to 1.9), and NT-proBNP ≥5,000 ng/L (HR 3.4, 95% CI 2.1 to 5.6) were significant predictors of long-term survival, whereas AF was not a multivariable long-term predictor (Table 2).

The amount of patients in NYHA class I or II was similar at baseline (AF 12%, non-AF 14%, p = 0.31). After 1 month, 64% of the patients with AF was in NYHA class I or II, in contrast to 77% of the patients without AF (p = 0.001) (Figure 2). But the improvement of patients with AF, from 12% in NYHA class I or II to 64%, was still significant (p = 0.001). Logistic regression showed that AF remained a significant predictor for NYHA III or IV after 1 month (odds ratio 1.7, 95% CI 1.0 to 2.8, p = 0.045), even after adjustment for age, gender, chronic obstructive pulmonary disease, tricuspid regurgitation, NYHA at baseline, left ventricular function, MR at discharge, and MR recurrence.

The stroke incidence appeared not to be significantly different with 1.8% for patients with AF and 1.0% for patients without AF (p = 0.40). No determinants for stroke could be identified. Incidence of ischemic and hemorrhagic strokes and stroke-free survival curves of patients with and without AF treated with MitraClip are shown in the supplementary materials (Supplementary Table S1 and Supplementary Figure S1).

Discussion

Patients with AF had MitraClip implantations benefits similar to non-AF patients in terms of 1-year survival. However, the majority of AF patients remained more symptomatic than patients without AF. Therefore, expectations in symptom reduction in AF patients should be reduced.

Current findings regarding survival were influenced by differences in baseline characteristics. Patients with AF were on average 5 years older than patients without AF and had higher levels of NT-proBNP. AF appeared not be a long-term predictor in multivariate analysis, in contrast to age and NT-proBNP. No differences in estimated 5-year survival were shown per subgroup after stratification of the patients by age (Supplementary Table S2). Regarding the effect of the MitraClip on the symptoms, it can be stated that logistic regression, however, showed that AF remained a significant predictor for NYHA III or IV after 1 month. Many other confounding factors are present, and AF is often a marker for more advanced heart disease and heart failure in general. AF can be a consequence of MR or, conversely, long-standing AF can lead to left atrial and mitral annular dilation, which causes MR. In regard to former published studies, our patients were comparable in baseline characteristics, for example, in age, gender, Logistic European System for Cardiac Operative Risk Evaluation (EuroSCORE), and left ventricular

Table 2
Predictors of mortality in multivariable analysis

Variable	All patients	Multivariable analysis	
	(n = 618)	HR (95% CI)	p value
Age at procedure (years)	74 ± 11		
<60	59 (10%)	1	
60–69	122 (20%)	1.4 (0.7–3.0)	0.39
70–79	233 (38%)	2.7 (1.3–5.3)	0.005
≥80	204 (33%)	2.8 (1.4–5.7)	0.003
Men	353 (57%)	1.4 (1.0–1.9)	0.037
Atrial fibrillation	326 (53%)		0.21
Coronary artery disease	357 (58%)		0.71
N-terminal pro-B-type natriuretic peptide (ng/L)	1642 (600–3669)		
<500	72 (12%)	1	
500–1999	131 (21%)	1.3 (0.8–2.1)	0.32
2000–4999	170 (28%)	1.6 (1.0–2.7)	0.052
≥5000	242 (39%)	3.4 (2.1–5.6)	<0.001
Estimated glomerular filtration rate (ml/min/1.73 m2)	56 ± 23		
<30	127 (21%)		
30–44	218 (35%)		0.80
45–59	159 (26%)		0.26
≥60	103 (17%)		0.137
Mitral regurgitation grade 4	406 (66%)	1.6 (1.1–2.2)	0.009
Tricuspid regurgitation grade 4	62 (10%)	1.6 (1.1–2.4)	0.023
Impaired left ventricular function (<30%)	227 (37%)		0.15

ejection fraction.[17,18,20] However, the mean age in the Endovascular Valve Edge-to-Edge Repair Study (EVEREST II) study was 67 years, and the majority of their patients had degenerative MR.[17] The mean age in our cohort was 74 years and the majority of our patients had functional MR, with no significant differences between patients with or without AF.

A similar percentage of AF patient had degenerative mitral valve disease compared with non-AF patients, as was procedural success rates. In accordance with previous studies, procedural success was equal.[17,18,20]

Most previous studies limited their analyses to 1-year survival after MitraClip treatment. Two studies showed similar 1-year survival rates for patients with and without AF,[17,18] while 1 study reported worse 1 year survival for patients with AF.[20] The differences in age and etiology between the EVEREST II study and our study can be an explanation for the difference in survival after MitraClip implantation. Factors as age appeared to be more important for life expectancy than AF. A previous study, based on the same population, proposed a risk model based on multiple factors of the baseline characteristics to enhance the patient selection.[22] A comparison of outcomes with previous studies is visualized in Table 3. Median follow-up duration in the current literature varies between 6 months and 1 year; our median follow-up was 1.8 years.

Patients with AF remained more symptomatic after MitraClip treatment compared with those without AF. Nonetheless, symptoms were reduced significantly after MitraClip treatment. It is difficult to investigate whether symptoms originated from the AF, the MR, or both as studies comparing rate-control versus rhythm-control showed that presence of AF was associated with worse a NYHA class and that NYHA class worsened over time.[23] There are conflicting findings on symptom reduction in patients with or without AF after MitraClip treatment (Table 3). The EVEREST II demonstrated that a significantly different percentage of patients were in NYHA class I or II at 12 months, being more present in people without AF.[17] By contrast, another study showed a similar improvement in NYHA class.[18] Besides, the TRAnscatheter Mitral valve Interventions (TRAMI) study also concluded that the majority of the patients were in NYHA class I or II after 1 month, but this was not statistically compared and seemed different (AF 58%, non-AF 71%).[20] Explanations for discrepancies in MitraClip literature regarding

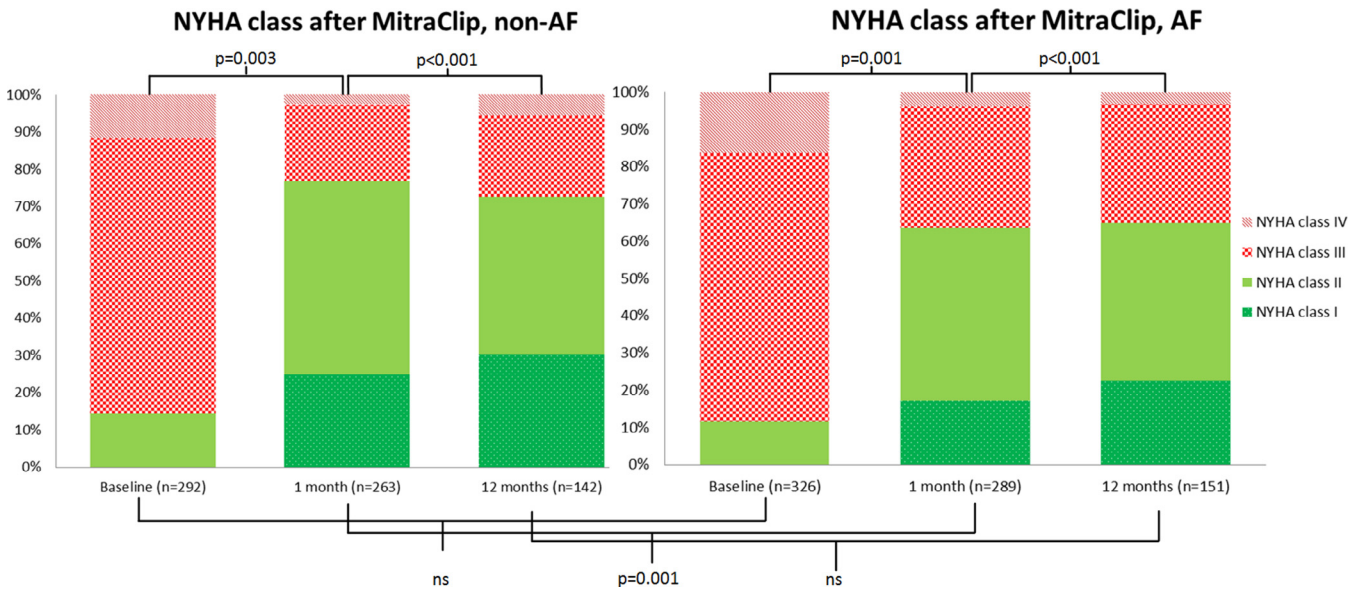

Figure 2. NYHA class after MitraClip implantation. The NYHA class after the MitraClip implantation of patients with (n = 326) and without (n = 292) AF. AF = atrial fibrillation; NYHA = New York Heart Association.

Table 3
Comparison with previous studies

Authors	Year	n	Survival				Symptoms NYHA class				Stroke incidence			
			Follow-up	AF	Non-AF	p-value	Follow-up	AF	Non-AF	p-value	Follow-up	AF	Non-AF	p-value
Herrmann et al.	2012	264	12m	100%	96%	0.23	I or II after 12m	89%	97%	0.02	1m	2.2%	0.8%	n.c.
Giordano et al.	2015	116	Median 6m	73%	90%	0.09	Improvement median 6m	61%	51%	0.50	Median 6m	0%	0%	n.a.
Jabs et al.	2017	760	12m	75%	84%	<0.05	I or II after 1m	58%	71%	n.c.	12m	1.5%	3.0%	n.s.
Velu et al.	2017	618	12m	82%	85%	0.30	I or II after 1m	64%	77%	0.001	Median 22m	2.1%	1.0%	0.40

m = month(s); n.a. = not applicable; n.c. = not calculated; n.s. = not significant.

the mortality and symptom reduction may be explained by the extreme heterogeneity of the patient population. A MitraClip treatment is suitable both for old and vital as well as for young and diseased patients.

Stroke incidence during follow-up appeared not to be significantly different between AF and non-AF patients in our cohort. This finding is important because of concerns regarding thrombus formation after MitraClip implantation. Current literature emphasizes the risk of thrombus formation after describing a case with acute left atrial spontaneous echocardiographic contrast and suspicious thrombus formation during a MitraClip procedure.[24]

This study was limited by the fact that the data were collected by several physicians. Despite the strict definitions, the interpretation of variables may differ. AF was not subclassified because the registry did not include differentiation in AF-type. Rehospitalization rates were not investigated because patients were often rehospitalized peripherally. The echocardiographic data were not adjudicated in a core laboratory, but analyses were conducted by highly experienced physicians. Some known predictors of mortality or symptoms were not included, which could lead to confounding.

Patients with AF remained more symptomatic after MitraClip treatment compared with non-AF patients. However, the majority of patients with AF still had symptom reduction after MitraClip treatment. One-year survival, MR reduction, and stroke incidence were similar in patients with AF to patients without AF detected. Therefore, AF patients should not be denied treatment with MitraClip, although expectations in symptom reduction should be reduced.

Disclosures

J. Baan Jr is proctor for Abbott Vascular MitraClip and receives an unrestricted research grant from Abbott Vascular. K.T. Koch is proctor for Abbott Vascular MitraClip. M.J. Swaans is proctor for Abbott Vascular MitraClip. J.A.S. Van der Heyden is proctor for Abbott Vascular MitraClip and Boston Lotus Valve. The other authors have no conflicts of interest to declare.

Supplementary Data

Supplementary data related with this article can be found, in the online version, http://dx.doi.org/10.1016/j.amjcard.2017.08.022.

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